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09/467,901	12/21/1999	JOOST VAN NEERVEN	02405.0190	2936

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EXAMINER	
DO, PENSEE T	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/467,901	NEERVEN, JOOST VAN	
	Examiner	Art Unit	
	Pensee T. Do	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is indefinite for reciting in the preamble "simulating in vivo interactions". What "in vivo interactions" are being simulated? Furthermore, since the body of the claim fails to recite any steps for simulating in vivo interactions, it is unclear of how the steps in the method are related to "simulating in vivo interactions". Although the last part of the claim refers to the function of the "in vivo simulation", it is still not a step.

Maintained Rejection(s)

Claim Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8-14, 16, 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) further in view of Johnson et al. (US 6,034,066) and Frank et al. (US 6,060,326).

Johansen et al. teach a method of detecting an antibody in a sample using a labeling compound and comprising the steps of mixing the ligand antigen, antibody or hapten bound to biotin with the sample; an antibody is directed against the antibody to be detected bound to a paramagnetic particles; and a chemiluminescent acridinium compound bound to avidin or streptavidin to form a solid phase complex; separating the solid phase from the liquid phase; and analyzing the separated solid phase for the presence of chemiluminescent complex. There are several embodiments. In one embodiment, the method comprises the following steps: mixing the ligand antigen, antibody or hapten bound to biotin or a functional derivative thereof with the samole and the antibody directed against the antibody to be detected bound to paramagnetic particles to form a first solid phase complex; adding a chemiluminescent acridinium compound covalently bound to avidin, streptavidin or a functional derivative thereof to form a second solid phase complex; magnetically separating the solid phase from the liquid phase; initiating the chemiluminescent reaction, and analyzing the separated solid phase for the presence of the chemiluminescent complex. Johansen et al. also teaches the method for the quantification of specific antibodies, such as immunoglobulins, wherein a truly parallel reference immunoassay using an identical protocol as a reference. The method comprises measuring the concentration and/or the relative contents of a specific antibody in a liquid sample, wherein the measured light emission

of a separated solid phase comprising a captured specific antibody coupled to a chemiluminescent label is compared with the measured light emission obtained in a parallel reference immunoassay wherein the total contents of the class of antibodies in the sample to which said specific antibody belongs is measured. The method comprising the steps of mixing a ligand antigen, hapten towards which the specific antibody to be measured is directly bound to biotin or a functional derivative thereof; an antibody directed against the constant portion of the antibody to be measured bound to paramagnetic particles and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof with the sample to form a first solid phase from the liquid phase; magnetically separating the first solid phase from the liquid phase; initiating a chemiluminescent reaction and measuring the light emission of the separated first solid phase; mixing a ligand antibody directed against the class of antibodies to be measured bound to biotin or a functional derivative thereof ; an antibody directed against the constant portion of the class of antibodies to be measured bound to paramagnetic particles ; and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof wherein the term total shall mean the entire amount of the designated class of immunoglobulins (e.g. IgA, IgE, etc.) With the sample to form a second solid phase complex, magnetically separate the second solid phase form the liquid phase; initiating the light emission of the separated first solid phase with that of the separated second solid phase. The specific antibody to be measured in the sample is preferably a specific immunoglobulin selected from the group

consisting of IgA, IgD, IgE, IgG, IgM and subclasses thereof. (See col. 3, line 30-col. 5, line 45).

However, Johansen et al. fails to teach using an IgE receptor to bind IgE antibody/ligand complexes and a method of quantification of IgE wherein the IgE to be detected is quantified using both CD23 alone to obtain a first measurement and using FcORII alone to obtain a second measurement. Johansen fails to teach a "method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody or a hapten in a liquid sample suspected to contain the IgE antibody by simulating in vivo interactions between IgE antibody, the IgE antibody's ligand and the IgE antibody's receptor".

Johnson et al. teach multiple important roles of CD23 in the regulation of immune responses, particularly the regulation of IgE responses. Among these roles, CD23 acts as a cellular receptor for IgE and is found in various cell types including B cells. (See col. 1, line 31-col. 2, line 64).

Frank et al. teach detecting IgE antibodies using a human Fc epsilon receptor FcOR. (See col. 1, line 45-col. 2, line 10).

It would have been obvious to one of ordinary skill in the art to use the IgE receptors of Johnson et al. and Frank et al. to measure IgE according to the method of Johansen et al. since both of these receptors, CD23 and FcOR, are specific to IgE antibody and because FcOR and CD23 can bind to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. (See Frank et al. Col. 1, lines 19-34). Regarding claim 16, wherein the number of ligand molecules is between 100% and

200 % of the number of IgE molecules to be detected, it would have been obvious to one of ordinary skills in the art to use enough ligand molecules to optimize binding of all the IgE molecules to be detected. In order to detect 100% of the IgE present in the sample, at least 100% of ligand molecules must be present to bind all the IgE present in the sample. Regarding claim 23, in view of the 112, 2nd paragraph, the preamble "simulating in vivo interactions" is not given any patentable weight.

Claims 6, 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) in view of Frank et al. (US 6,060,326) further in view of Arnold, Jr. et al. (US 6,004,745).

Johansen et al. and Frank et al. have been discussed above.

However, Johansen and Frank fail to teach adding label after a first separation step and a second separation to separate the non-complexed labels.

Arnold, Jr. discusses in the background section that a typical sandwich assay involve incubating an immobilized antibody (IgE receptor) with a test medium (sample). Antigens, if in the medium, will bind to the antibody. After incubation, unbound antigen is removed in a separation step. After a second, or simultaneous incubation with a solution of labeled antibody, the bound antigen becomes sandwiched between the immobilized antibody and the labeled antibody. After a second separation step, the amount of labeled antibody can be determined as a measure of the antigen in the medium. (see col. 1, lines 55-66).

It would have been obvious to one of ordinary skill in the art to add the label molecule after a first separation step and then separating the non-complexed labels as

discussed in Arnold, Jr. using the reagents in the method of Johansen modified by Frank because such second separation steps, although time consuming, increases the sensitivity of the assay results. Furthermore, since the non-complexed immobilized antibody and the non-complexed labels are separated one at a time, cross-reactivity between the label and the immobilized antibody/reagent is eliminated.

Response to Arguments

Applicant's arguments filed on January 7, 2005 have been fully considered but they are not persuasive.

Regarding the 103 rejection by Johansen in view of Johnson and Frank 2., Applicant argues that Johansen and Frank 2 do not use the same set of reagents, Johansen uses antibodies to detect the presence of IgE, not IgE receptors. In contrast, Frank 2 uses at least an IgE receptor and may or may not use other reagents like antibodies to bind different portions of an IgE molecule. Johnson merely provides a discussion as to the functions of CD23 in the immune system without any reference to using this receptor in the method of detecting or quantifying IgE. Thus, Applicant argues that the Office improperly uses hindsight in suggesting that it would have been obvious to use CD23 or FccR in the method of Johansen or that it would have been obvious to optimize detection or quantification by binding all the IgE molecules in the samples. Applicant's final argument pertains to a lack of reasonable expectation of success. Applicant argues that Johansen and Frank 2 use different steps and different reagents in their methods and that the Office has not provided evidence to suggest that there was an expectation that one could successfully extrapolate the use of reagent (FccR1

receptor) utilized under a particular set of conditions (Frank 2) and expect it to work as a replacement of another reagent (anti-IgE antibody) under a different set of conditions (Johansen). And Johnson does not mention the use of an IgE receptor in the method of detecting an IgE antibody. Applicant also mentions that the Fc receptor taught by Frank 2 is a canine receptor, not a human Fc receptor.

Frank 2 in col. 5, lines 47-56 teaches that :

> In addition, a Fc.sub..epsilon. R formulation of the present invention can include not only a Fc.sub..epsilon. R but ***also one or more additional antigens or antibodies useful in detecting IgE***. As used herein, an antigen refers to any molecule capable of being selectively bound by an antibody. As used herein, specific binding of a first molecule to a second molecule refers to the ability of the first molecule to preferentially bind to (e.g., have higher affinity higher avidity for) the second molecule when compared to the ability of a first molecule to bind to a third molecule. The first molecule need not necessarily be the natural ligand of the second molecule. ***Examples of antibodies used in the present invention include, but are not limited to, antibodies that bind selectively to the constant region of an IgE heavy chain (i.e., anti-IgE isotype antibodies) or antibodies that bind selectively to an IgE having a specific antigen specificity (i.e., anti-IgE idiotypic antibodies).*** Examples of antigens used in the present invention include any antigen known to induce the production of IgE. Preferred antigens include allergens and parasite antigens.

In col. 2, lines 11-17, teaches that:

> "The invention relates to the discovery of purified, high affinity canine Fc eplison receptor can be used in canine eplison immunoglobulin (referred to herein as IgE or ***IgE antibody***) ***–based detection methods*** and kits."

And in col. 8, lines 50-56, teaches that :

> "A complex can be detected in a variety of ways, including: ....**particulate-based assay (using particulates such as magnetic particles...).**

Such teaching indicates that Frank 2 uses the same assay method (assay using paramagnetic particles) as of Johansen to detect IgE antibody. The reagents in Frank

are a ligand (antibody, antigen or a hapten), an IgE receptor (Fc eplison receptor), a carrier/particulate (magnetic particles in a magnetic particle-based assay) and IgE antibodies in sample to be detected. However, Johansen teaches using the same reagents in a more explicit method steps. Furthermore, if Frank 2 teaches the same method and reagents as in Johansen, then Frank 2 would be applied to a 102 rejection instead of 103 rejection. Applicant fails to point out any factors that would prevent the combined references from having a reasonable expectation of success.

The motivation to combine the references has been clearly established in the previous office action. Johansen teaches a method for the quantification of specific antibodies such as immunoglobulins (IgE, IgA, ..). The sample containing the specific antibody is mixed with a ligand antigen (free dissolved ligand of the present invention); an antibody directed against a constant portion of the antibody to be measured bound to a paramagnetic particles and a chemiluminescent acridinium compound as a label; magnetically separating the bound from the unbound; and detect. Johnson uses a CD23 (a reagent directed against a constant portion of the antibody to be measured (IgE antibody)), which is specific for IgE antibody being detected. Frank teaches detecting IgE antibodies using a human Fc epsilon receptor (Fc0R). Such Fc eplison receptor is specific to the IgE of the IgE antibody being detected. Thus, it would have been obvious to one of ordinary skill in the art to use CD23 or Fc0R as an IgE receptor to measure IgE antibody because these receptors can bind to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. Regarding claim 16, it is obvious for an ordinary skill in the art to optimize the result by binding all the IgE mocecules to

be detected. Regarding Applicants' analysis of the two references about "solid supports vs. suspension of particles", it is well known that solid supports can include particles and Frank teaches that his reagents can be detected using particulate-based immunoassay (particulates such as magnetic particles, polystyrene, latex beads). Furthermore, whether a solid support or a particles is used, the antibody/ligand must bind to the solid support or a particle and a step of capturing must be performed. Thus, there is no difference between the reagents of the two methods.

Since the deficiencies, as submitted by the Applicants, in Frank and Johansen have been explained and cure. It is unnecessary to discuss the reference by Johnson.

Regarding the 103 rejection by Johansen in view of Frank 2 and Arnold, Applicants argue that Arnold does not cure the deficiency of motivation as discussed above. Arnold's method does not use an IgE receptor or mention the use of an IgE receptor. Rather, Arnold uses two antibodies, one immobilized to a surface and the other labeled. With respect to claims 17-19, the Office has not explained why one skilled artisan would replace only the immobilized antibody with an IgE receptor to arrive at the present invention instead of replacing both antibodies, which as alleged by the Office, may provide more specificity and sensitivity to the method.

Since the so-called "deficiencies" of Frank 2 and Johansen have been discussed above. It is unnecessary for Arnold to cure those deficiencies. Since Arnold teaches that solution of labeled antibody is to be applied after the first separation step (see previous office action page 7 following a separation step, Arnold teaches "after a second, or simultaneous incubation with a solution of labeled antibody, the bound antigen becomes

sandwiched ..."). Such label solution, taught by Johansen, comprises a chemiluminescent acridinium compound covalently bound to avidin, streptavidin or a functional derivative thereof to form a second solid phase complex. Arnold is relied upon for the separation steps. Separation steps are known in the art for eliminating non-specific bindings, cross-reactivity and increasing sensitivity of the assay results. One of ordinary skills in the art would have been motivated to use two separation steps because the first separation is to eliminate non-bound carrier (immobilized antibodies) and the second separation step is to eliminate non-bound labels. In any sandwich assay wherein the reagents (immobilized antibodies and then labels) are added one at a time, separation steps must be performed after each addition of each reagent (immobilized antibodies and labels). These separation steps are well known in the art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 571-272-0819. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pensee T. Do
Patent Examiner
March 25, 2005

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641
4/4/05